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Transient Grades 3 to 4 Acute Hepatitis Is a Common Complication of Rabbit Antithymocyte Globulin (Thymoglobulin) Administered before Allogeneic Stem Cell Transplantation

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A B S T R A C T

Because antithymocyte globulin (ATG) is increasingly used to prevent graft-versus-host disease (GVHD), we performed a retrospective study in adult patients transplanted at our center between January 2008 and December 2012 to explore incidence, characteristics, potential risk factors, and consequences of severe acute hepatotoxicity (SAH) of rabbit ATG (Thymoglobulin) defined as a grade 3 to 4 increase of transaminases. Two hundred twelve patients were included. SAH was diagnosed in 55 patients, representing an incidence of 26%. SAH occurred at a median time of 2 days (range, 1 to 3) after ATG administration, reaching maximum median levels of aspartate aminotransferase and alanine aminotransferase of 8.7 × upper limit of normal (ULN; range, 1.2 to 160) and 11.7 × ULN (range, 4-100), respectively. The International Normalized Ratio was beyond the normal range in 44% of patients. Transaminases decreased below 2 × ULN after a median time of 9 days. We do not report any deleterious impact of SAH on survival, nonrelapse mortality, relapse, or GVHD. Blood systolic pressure < 90 mm Hg during administration of ATG and 2 previous autologous SCT were identified as risk factors for SAH. We believe physicians should be aware of this common toxicity immediately after the administration of ATG to avoid any potential hepatotoxic drug before the resolution and to prevent any risk of hemorrhagic accident.

INTRODUCTION

Antithymocyte globulin (ATG) is increasingly used before allogeneic stem cell transplantation (allo-SCT) to reduce incidence and severity of graft-versus-host disease (GVHD). Randomized studies in the myeloablative setting with unrelated donors have indeed reported reduced incidences of grades III to IV acute and extensive chronic GVHD, without increased relapse rates [1-4]. Unfortunately, comparable randomized studies are lacking in the reduced-intensity conditioning (RIC) setting. Optimal dose and schedule remain controversial, although available retrospective data seem to favor a dose of rabbit ATG (Thymoglobulin; Genzyme, Lyon, France) of 4.5 to 6 mg/kg administered on the last few days before transplantation [5]. Interestingly, a large retrospective study by the Center for International Blood and Marrow Transplant Research has challenged the use of ATG in the RIC setting, reporting an increased relapse risk adversely affecting overall survival (OS) [6]. These data clearly indicate that the use of ATG itself remains a matter of debate, at least in the RIC setting. Because of this debate, it is important to carefully evaluate all side effects of ATG and their potential consequences on transplant outcome.

The side effects of ATG are very common and well described as far as fever, chills, or hypotension are concerned [2,7]. Acute hepatotoxicity also exists, but its knowledge is limited by the scarcity of data. One case report of reversible acute hepatotoxicity induced by horse ATG in a patient with Fanconi anemia undergoing allo-SCT was reported [8]. Recently, 2 cases of severe transaminases elevation have been reported after rabbit ATG used in RIC allo-SCT [9]. Mild and transient elevation of bilirubin levels beyond the normal range have also been reported in 22.7% of patients after ATG

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(Fresenius, HemoCare Immune Therapy, Gräfelfing, Germany) without change in the level of transaminases [7]. Thus, to further explore incidence, characteristics, potential risk factors, and consequences of acute hepatotoxicity of ATG, we conducted a retrospective study of patients transplanted at our center between January 2008 and December 2012.

METHODS

Selection of Patients

All adult patients (≥18 years) with a first allo-SCT performed between January, 1, 2008 and December 31, 2012 at our center after a conditioning regimen incorporating rabbit ATG (Thymoglobulin) were eligible. Two hundred twelve patients fulfilling these criteria were included. All medical records were reviewed to ensure the quality of data.

The doses and schedules of ATG were 2.5 mg/kg on days −2 and −1 (n = 180); 2.5 mg/kg on day −1 (n = 10) or day −2 (n = 13); 2.5 mg/kg on days −3, −2, and −1 (n = 1); and 3.75 mg/kg on days −6, −5, and −4 (n = 8) depending on diseases and ongoing protocols. All patients received premedication with methylprednisolone (.5 mg/kg) and dexchlorpheniramine (5 mg i.v.) 30 minutes before and 4 hours after the start of ATG. They also received acetaminophen in case of fever, always at therapeutic doses (≤4 g/day). ATG was administered over 8 to 24 hours according to tolerance. All patients received low-dose heparin (100 UI/kg/day i.v.) and ursodeoxycholic acid (500 mg × 3/day, p.o.) from the beginning of the conditioning regimen for prevention of veno-occlusive disease.

During the study period, our strategy was to check liver function tests at least 3 times a week (Monday, Wednesday, and Friday) from the start of the conditioning regimen until discharge from hospital. Severe acute hepatotoxicity (SAH) was defined as aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN) within 1 week after administration of ATG (grade 3 or 4 toxicity according to the Common Terminology Criteria for Adverse Events, version 4.0).

Statistical Analysis

Patient- and disease-related characteristics of both groups (SAH versus no SAH) were compared using either the chi-square test or the Fisher test, as appropriate. OS was calculated from the date of transplantation to either the date of death from any cause or last follow-up. Event-free survival (EFS) was calculated from the date of transplantation to the date of relapse, progression, death from any cause, or last follow-up. Probabilities of OS and EFS were calculated using the Kaplan-Meier estimate [10], with the log-rank test for univariate comparisons.

Nonrelapse mortality (NRM) included all causes of death without prior relapse/progression, occurring at any time after transplant. Cumulative incidence curves were used for relapse incidence and NRM in a competing risk setting with death in complete remission as a competing event for relapse and relapse/progression as a competing event for NRM [11].

The Gray test was used for univariate comparisons. Cumulative incidence curves were used for GVHD in a competing risks setting, with death as a competing event. The analysis of risk factors for SAH was performed in a Cox proportional hazards model [12] in which pretransplant variables with $P < .15$ in the univariate analysis were considered and the least significant variables were excluded in a stepwise backward procedure until all remaining factors were significant at the $P = .05$ level. For multivariate analysis, all cases with at least 1 missing value in 1 of the variables considered were excluded. Statistical analyses were performed with R 2.13.2 software packages (R Development Core Team, Vienna, Austria).

RESULTS

Characteristics of Patients with SAH

As shown in Table 1, SAH was diagnosed in 55 patients, representing an incidence of 26%. The characteristics of patients with or without SAH are summarized in Table 2. The conditioning regimens of patients with SAH were fludarabine (30 mg/m^2/day for 5 days) with i.v. busulfan 0.8 mg/kg × 4/day for 2 days (n = 45) or 3 days (n = 1) or 4 days (n = 7), cyclophosphamide (50 mg/kg/day for 4 days) with 2-Gy total body irradiation (TBI; n = 1), and 2-Gy TBI (n = 1). The median time between the first day of ATG and SAH was 2 days (range, 1 to 3).

Eight to 13 episodes of SAH were diagnosed each year with different batches of ATG, excluding a batch effect. No patient had evidence of liver involvement by hematological disease at transplant. One female patient had chronic C hepatitis diagnosed 9 years before allo-SCT, with undetectable viral load at transplant. Before administration of ATG, transaminases were <2 × ULN in 51 patients and 2 to 3 × ULN in 4 patients. No patient was receiving azoles at the time of SAH. The maximum median levels of AST and ALT were 8.7 × ULN (range, 1.2 to 160) and 11.7 × ULN (range, 4 to 100), respectively. There was an associated mild elevation of bilirubin at a median level of 1.4 × ULN (range, .3 to 6.5). Further doses of ATG were not administered in 8 patients with a grade 4 toxicity diagnosed immediately after the first dose.

All patients had fever and blood cultures during administration of ATG. One patient had a positive blood culture for *Enterococcus* sp. No patient was diagnosed with viral hepatitis (A, B, C, Epstein-Barr virus, cytomegalovirus, or adenovirus) during SAH.

The International Normalized Ratio (INR) was >1.3 in 24 patients (median, 1.8; range, 1.32 to 3.78). In 19 patients with grade 4 toxicity, 12 (63.1%) had an INR > 1.3 (median, 2.1; range, 1.32 to 3.78). In the 36 patients with grade 3 toxicity, 12 (33.3%) had an INR > 1.3 (median, 1.7; range, 1.33 to 2.58). The INR normalized in less than 1 week in all patients without any hemorrhagic accident.

No patient developed encephalopathy or died of liver failure. No hepatic biopsy was performed. Liver function tests improved in all patients with both transaminases < 5 and <2 × ULN at median times of 5 days (range, 1 to 19) and 9 days (range, 3 to 22), respectively. For grade 3 toxicity, these figures were 2 days (range, 1 to 19) and 7 days (range, 3 to 22) and for grade 4 toxicity, 9 days (range, 6 to 15) and 15 days (range, 10 to 20). No patient developed veno-occlusive disease or hepatic acute GVHD. One female patient aged 59 years developed hepatic chronic GVHD 11 months after transplant.

Consequences of SAH on Transplant Outcome

In SAH versus no SAH groups, the number of primary engraftment failures were 5 (9.1%) versus 12 (7.6%), $P = .77$. Median times to neutrophil engraftment to .5 × 10^9/L and platelet engraftment to 50 × 10^9/L in SAH versus no SAH groups were 18 days (range, 6 to 31) versus 17 days (range, 10 to 40) and 13 days (range, 9 to 120) versus 13 days (range, 0 to 100), respectively.

As shown in Figure 1, with a median follow-up of 43 months (range, 11 to 76), the 3-year OS and EFS rates in SAH

Table 1
Levels of Transaminases during or within 1 Week after Conditioning

AST and/or ALT	0 ≤1 ULN	Grade 1 > 1-3 ULN	Grade 2 > 3-5 ULN	Grade 3 > 5-20 ULN	Grade 4 > 20 ULN
Conditioning with ATG (n = 212)	106 (50)	24 (11.3)	27 (12.7)	36 (17)	19 (9)
Conditioning without ATG* (n = 198)	160 (80.8)	33 (16.7)	4 (2)	1 (.5)†	0

Values in parentheses are percents. Grades are defined according to the Common Terminology Criteria for Adverse Events, version 4.0.

* Control group of patients transplanted during the same period of study.

† This patient had a focal nodular hyperplasia of the liver and received myeloablative conditioning with Bu-Cy.

Table 2
Characteristics of Patients with or without SAH

	SAH (n = 55)	No SAH (n = 157)	*P*
Age, yr			
Median (range)	58 (21-65)	57 (19-67)	
≥55	38 (69.1)	93 (59.2)	.26
Sex			.045
Male	27 (49.1)	103 (65.6)	
Female	28 (50.9)	54 (34.4)	
Diseases			
AML	13 (23.6)	58 (36.9)	.10
ALL	3 (5.5)	9 (5.7)	1
NHL	8 (14.5)	23 (14.7)	1
HOD	5 (9.1)	6 (3.8)	.16
MM	13 (23.6)	18 (11.5)	.048
MDS	5 (9.1)	18 (11.5)	.80
AA	1 (1.8)	7 (4.5)	.68
CLL	4 (7.3)	12 (7.6)	1
MPS	3 (5.5)	6 (3.8)	.70
Status at transplant			
CR1 or PR1 or chronic phase	23 (41.8)	61 (38.8)	.82
>CR1 or >PR1	23 (41.8)	51 (32.5)	.28
Untreated	3 (5.5)	18 (11.5)	.29
Refractory	6 (10.9)	27 (17.2)	.37
Previous treatment with GO	2 (3.6)	2 (1.3)	.28
Number of previous auto-SCT			
1	18 (32.7)	41 (26.1)	.44
2*	7 (12.7)	2 (1.3)	.001
Median time between last auto-SCT and allo-SCT, mo, (range)	20 (2-142)	17 (2-187)	
Conditioning regimen†			.03
NMA	1 (1.8)	0	
RIC	46 (83.6)	113 (72)	
MAC	8 (14.6)	44 (28)	
Donors			.49
Related	26 (47.3)	64 (40.8)	
Unrelated	29 (52.7)	93 (59.2)	
Female donor/male recipient	11 (20)	44 (28)	.32
Source of stem cells			.12
PB	54 (98.2)	144 (91.7)	
BM	1 (1.8)	13 (8.3)	
Number of CD34$^+$ cells ($\times 10^6$/kg)			
Median (range)	6.3 (2.1-21.7)	6.3 (1.3-31.9)	
≥6.3	28 (50.9)	82 (52.2)	.99
Prophylaxis of GVHD			
CsA	23 (41.8)	62 (39.5)	.89
CsA+methotrexate	24 (43.6)	72 (45.8)	.89
CsA+MMF	8 (14.6)	22 (14)	1
MMF+steroid	0	1 (0.7)	1
Blood systolic pressure < 90 mm Hg during administration of ATG			.001
Yes	22 (40)	30 (19.1)	
No	18 (32.7)	93 (59.2)	
Missing data	15 (27.3)	34 (21.7)	
AST and/or ALT toxicity before ATG‡			.81
Grade 0	43 (78.2)	127 (80.9)	
Grade 1	12 (21.8)	30 (19.1)	

AML indicates acute myeloid leukemia; ALL, acute lymphoid leukemia; NHL, non-Hodgkin lymphoma; HOD, Hodgkin disease; MM, multiple myeloma; MDS, myelodysplastic syndrome; AA, aplastic anemia; CLL, chronic lymphoid leukemia; MPS, myeloproliferative syndrome; CR, complete remission; PR, partial remission; GO, gemtuzumab ozogamicin; NMA, nonmyeloablative; MAC, myeloablative conditioning; PB, peripheral blood; BM, bone marrow; CsA, cyclosporine A; MMF, mycophenolate mofetil.
Values in parentheses are percents, unless otherwise noted.
* Multiple myeloma (n = 8) and myelodysplastic syndrome (n = 1).
† According to Bacigalupo et al. Biol Blood Marrow Transplant 2009;15:1628-1633.
‡ According to the Common Terminology Criteria for Adverse Events, version 4.0.

versus no SAH groups were 65.7% ± 6.7% versus 53.7% ± 4.1% (*P* = .1) and 49.3% ± 7% versus 49.7% ± 4% (*P* = .65), respectively. The 3-year NRM and relapse incidence in the same groups were 5.4% ± 3.1% versus 15.6% ± 2.9% (*P* = .08) and 45.2% ± 7% versus 34% ± 3.9% (*P* = .35), whereas the cumulative incidence of acute GVHD grades II to IV and extensive chronic GVHD were 21.8% ± 5.6% versus 36.9% ± 3.9% (*P* = .052) and 10.9% ± 4.2% versus 15.4% ± 2.9% (*P* = .39), respectively.

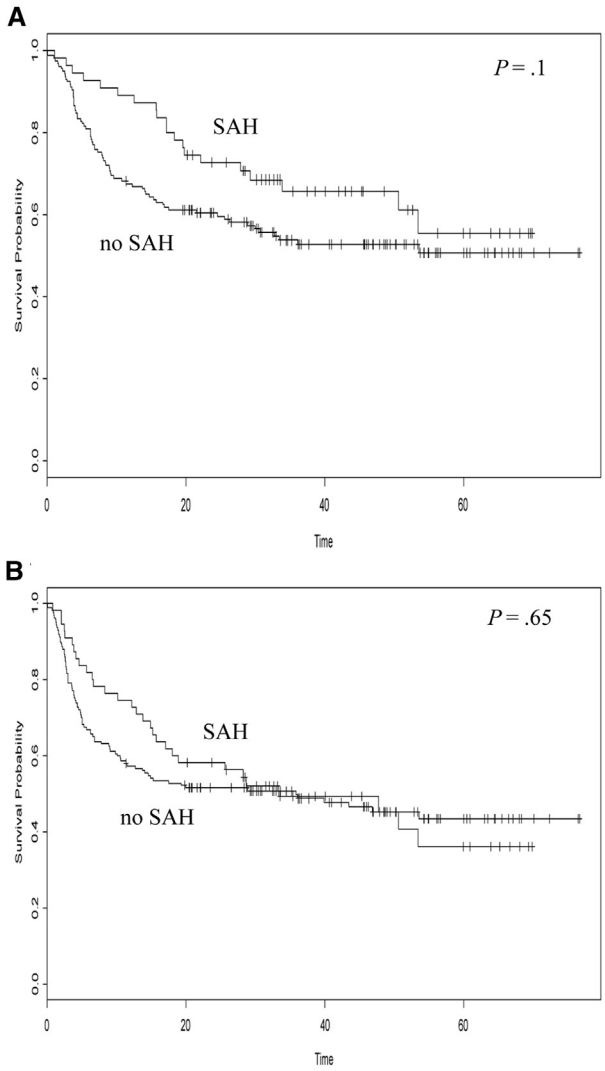

Figure 1. OS (A) and EFS (B) in SAH and no SAH groups.

Risk Factors for SAH

As shown in Table 2, pretransplant characteristics of both groups (SAH versus no SAH) were comparable except for sex, multiple myeloma, existence of 2 previous autologous (auto-) SCTs, conditioning regimen, blood systolic pressure < 90 mm Hg during administration of ATG, and a trend for acute myeloid leukemia. As shown in Table 3, the multivariate analysis identified blood systolic pressure < 90 mm Hg during administration of ATG and the existence of 2 previous auto-SCTs as significant risk factors for SAH.

DISCUSSION

In the present study, the incidence of SAH after administration of ATG (Thymoglobulin) was 26%. Because ATG is increasingly used, it is important to report such a common toxicity. We do not report any fatal liver failure, but nearly half of our patients had a transient increased INR. The

Table 3
Risk Factors for SAH: Multivariate Analysis

Variable	Hazard Ratio	95% Confidence Interval	*P*
Existence of 2 previous auto-SCTs	5.11	4.67-5.55	.0002
Systolic pressure < 90 mm Hg during ATG	3.06	2.74-3.38	.0004
Female sex	1.48	1.15-1.82	.24
AML	.65	.27-1.03	.26
RIC or NMA regimen	1.54	1.09-1.99	.34
MM	1.35	.89-1.81	.52

transaminases normalized in all patients. There was no deleterious impact on OS, EFS, NRM, relapse, or GVHD. The trend for a lower incidence of acute GVHD grades II to IV in the SAH group might be explained by higher frequencies of related donors and RIC regimens together with a lower frequency of the female donor/male recipient combination. We also identified blood systolic pressure < 90 mm Hg during administration of ATG and existence of 2 previous auto-SCTs as significant risk factors for SAH. However, because most patients with 2 previous auto-SCTs had a multiple myeloma, we cannot rule out that double auto-SCT may be a surrogate marker of this disease.

The studies reporting on acute hepatotoxicity of ATG in the allo-SCT setting are rare. One case of a young female patient with Fanconi anemia who received horse ATG as part of conditioning before transplant was reported in 2007 [8]. The patient developed an asymptomatic elevation of AST (17.7 × ULN) and ALT (12 × ULN) at day 5 before transplant. The ATG was stopped and the liver function tests improved without recurrence of toxicity after replacement with rabbit ATG [8]. Recently, 2 cases of female patients who developed a transient severe transaminase elevation after receiving rabbit ATG before allo-SCT were reported. The AST peaked at 1286 and 1212 U/L and the ALT at 991 and 689 U/L. In both cases, the hepatitis quickly resolved without any complication [9]. In 2002, the impact of ATG (Fresenius) was studied by Pihusch et al. [7]. They reported bilirubin levels beyond the normal range in 22.7% of patients, without change in the level of transaminases in most patients in contrast to our study. The different cellular targets used to produce both rabbit ATG (Jurkat cell line for Fresenius and human thymocytes for Thymoglobulin) may account for differences in antibodies composition and thus reported toxicities.

Several arguments support the responsibility of ATG in the reported acute hepatotoxicity. It is indeed very unlikely that SAH be related to other drugs in conditioning regimens like fludarabine, i.v. busulfan, or cyclophosphamide. During the study period, 98 allo-SCTs were performed after a myeloablative conditioning with cyclophosphamide 60 mg/kg/day for 2 days and i.v. busulfan .8 mg/kg × 4/day for 4 days (Bu-Cy; n = 57) or 12-Gy TBI (TBI-Cy, n = 41) with only 1 episode of SAH during a conditioning with Bu-Cy in a patient with a focal nodular hyperplasia of the liver. We did not observe any SAH in 33 patients transplanted after the nonmyeloablative conditioning regimen combining fludarabine (30 mg/m^2/day for 3 days) and 2-Gy TBI.

As additional evidence, 46 patients were transplanted with cord blood units after a RIC regimen combining fludarabine (40 mg/m^2/day for 5 days), cyclophosphamide (50 mg/kg), and 2-Gy TBI without any episode of SAH. Furthermore, the liver toxicity of Bu-Cy and inverted Cy-Bu was studied by Cantoni et al. in 2011 [13]. They reported AST and/or ALT beyond the normal range between day +10 and day +30 after transplant and always < 5 × ULN. This is in sharp contrast with our study where SAH was diagnosed at a median time of 2 days after the start of ATG. Finally, we cannot incriminate the premedication of ATG or acetaminophen either, because these drugs are commonly used without ATG in many other circumstances in our unit without ever observing such acute hepatotoxicity. Moreover, although severe hepatotoxicity of acetaminophen has almost exclusively been reported after over-dosages [14], acetaminophen was always used in our study at therapeutic doses (≤4 g/day).

The mechanisms underlying acute hepatotoxicity of rabbit ATG remain undetermined, and the design of our study precludes any conclusion. However, the rapid reversibility of the phenomenon reported in our study does not support a direct toxic effect of ATG on hepatocytes because ATG has a long mean elimination half-life of 30 days in human plasma [15,16]. The identification of blood systolic pressure < 90 mm Hg during ATG administration as a significant risk factor for SAH raises the hypothesis of a clinical syndrome close to the shock liver. The shock liver is indeed characterized by a sudden elevation of AST and ALT in response to cellular anoxia, followed by a rapid resolution within 7 to 10 days [17]. This is very similar to the toxicity observed in our study where the transaminases peaked at a median time of 2 days after the start of ATG and resolved (<2 × ULN) after a median time of 9 days. Finally, our study also identifies the existence of 2 previous auto-SCTs as a risk factor for SAH, suggesting that a heavily pretreated disease might be a favoring condition of a possible transient ischemic hepatitis caused by severe hypotension during administration of ATG.

Our study is the first to report the incidence of SAH after administration of ATG (Thymoglobulin) in the allo-SCT setting, and we believe physicians should be aware of this common risk to avoid as much as possible any other potential hepatotoxic drug in the immediate post-transplant period and also because some patients have an increased INR together with thrombocytopenia and sometimes heparin for veno-occlusive disease prophylaxis. Our data also suggest that severe hypotension during ATG administration should be a warning sign to check liver function tests. This knowledge may help avoid additional hepatotoxicity and prevent hemorrhagic accidents.

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